REMARKS

Claims 1, 5-7, 11-15, 18-21, 23-27, 33, 35-37, 42-44, 48-52, 54-56, 60, and 65 are pending. Claims 2-4, 8-10, 16-17, 22, 28-32, 34, 38-41, 45-47, 53, 57-59, and 61-64 are cancelled. Claim 66 is new.

Claims 1, 6, 7, 26-27, 33, 35, 37, 43-44, 56, 60, and 65 are currently amended. Support for these amendments is found throughout the specification. For example, support for the present amendments can be found in the claims as originally filed as well as in paragraphs [0020]-[0023], [0027]-[0029], [0048], [0054]-[0058], [0071]-[0075] and [0101]-[0108] of the specification. Support for newly added claim 66 can be found inter alia, in paragraphs [0083] and [0108]. These amendments raise no issue of new matter.

Applicants reserve the right to file one or more divisional or continuation applications directed to any cancelled or non-elected subject matter and claiming priority to the present application.

Oath/Declaration

The Examiner's consideration of the Kaufman and Bereta declaration filed on November 15, 2007 under 37 CFR 1.132 is acknowledged with appreciation.

Rejections under 35 U.S.C. § 112 1st ¶ - Enablement Requirement

Claims 33, 35-37, 42-44, 48-52, 54-56, 60, and 65 are rejected for lack of enablement. Although the Examiner acknowledges that the specification is "enabling for a method of targeting neoplastic cells," the Examiner alleges that the specification "does not reasonably provide enablement for a method of treating neoplasia… by administering via any route the composition comprising an attenuated Salmonella."

In reply, applicants traverse the rejection. The presently claimed invention is directed to a composition for delivering an agent to a neoplastic cell of a solid tumor expressing a neoplasm-specific antigen, wherein the composition comprises an agent and an attenuated *Salmonella* or *Shigella* microorganism that has an antibody or fragment thereof on its cell surface that binds to a neoplasm-specific antigen on the surface of a neoplastic cell of a solid tumor. The presently claimed invention is also directed to methods of treating a carcinoembryonic antigen (CEA)-

expressing neoplasia in a subject via administering a therapeutic composition of the attenuated *Salmonella* or *Shigella* microorganism of the invention, in the absence or presence of an agent.

Administration of Attenuated Salmonella Can Produce a Therapeutic Effect

The Office Action alleges that the "issue at hand is whether administering a therapeutic composition would result in therapeutic effect in treating any cancer or colon cancer" (See Page 6, line 4 of Office Action dated July 9, 2008). Without conceding the correctness of the Examiner's position, and to advance prosecution of this application, the present claims have been amended and are directed to administering an attenuated *Salmonella* or *Shigella* microorganism to treat a carcinoembryonic antigen (CEA)-expressing neoplasia, such as a breast tumor, a colon tumor, a lung tumor, a pancreatic tumor, and a stomach tumor, via dispersing the therapeutic composition of the invention to a subject via subcutaneous, intravenous, or oral delivery.

Applicants submit that a person of ordinary skill in the art would have been enabled to deliver a live bacterial vaccine by intravenous, subcutaneous, or oral delivery. For example, Toso et al. report "intravenous infusion of VNP20009 to patients with metastatic cancer," establishing the safe doses for systemic injection of VNP20009 in humans, and observed focal tumor colonization in 3 of 24 patients (Exhibit E; Toso et al., (2002) *J Clin Oncol.* 20(1):142-52). Furthermore, Medina and Guzman discuss that "use of live bacterial carriers constitutes a powerful tool to achieve an efficient delivery of either vaccine antigens or DNA vaccine constructs" (Exhibit F; page 1578, 1st column, 1st paragraph; Medina and Guzman (2001) *Vaccine* 19:1573-80).

Applicants note that papers published after applicants' filing date (Exhibit A; (2007) *Vaccine* 25(21):4183-92) confirm the therapeutic potential of an attenuated *Salmonella* microorganism that has an antibody or fragment thereof on its cell surface that binds to a neoplasm-specific antigen on the surface of a neoplastic cell of a solid tumor. For example, the 2007 paper by Bereta et al. shows that an attenuated *Salmonella* microorganism expressing an anti-CEA scFv binds to its CEA antigen *in vitro* (FIGS. 3 and 4 on pages 4187 and 4188, respectively). The attenuated *Salmonella* microorganism expressing the anti-CEA scFv also binds to the CEA antigen *in vivo* since it was observed that the microorganism accumulates in CEA expressing intestinal cells of CEA transgenic mice (FIGS. 5A-B on page 4189) and in

CEA-expressing tumors found on the right flank of mice (FIG. 5C on page 4189). Furthermore, administering a single $2x10^6$ cfu dose of the *Salmonella* microorganism by intravenous injection to mice bearing 7-day old colon carcinomas significantly reduced tumor growth, and completely inhibited tumor growth in 6 out of 10 mice (FIGS. 6A-B on page 4189). Thus, "genetically modified *Salmonella typhimurium* VNP20009 (VNP) is a useful vehicle for cancer therapy" (Bereta et al., (2007) *Vaccine* 25(21):4183-92).

The Examiner alleges that extrapolating effects of bacterial vector delivery in a rodent tumor model to tumor regression in any other subject is unpredictable. Applicants note that MPEP 2164.02 states that "'correlation' [of *in vivo* animal model assays to a claimed method of use] is dependent on the state of the prior art... if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." Furthermore, a rigorous exact correlation is not required. *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985).

In view of Kerbel et al. (Cancer Biology and Therapy (2003) 2 (supp 4): S134-139), applicants submit that a mouse model (a transgenic or nude mouse resulting in tumor formation) is routinely used as a model for the human condition and results in mice that can and are extrapolated to humans. For example, Kerbel et al. recognize that "a shift has occurred towards developing and using spontaneous mouse tumors arising in transgenic and/or knockout mice engineered to recapitulate various genetic alterations thought to be causative of specific types of respective human cancers," (abstract; Kerbel et al., (2003) *Cancer Biology and Therapy* 2 (supp 4): S134-139)). Therefore, results obtained using tumorigenic mouse models can be extrapolated to a subject suffering from a cancer and is sufficient for establishing a reasonable correlation between the Applicant's data pertaining to bacterial vector delivery in a rodent tumor model and tumor regression in another subject. Thus, the specification in combination with the state of the art at the time of the invention would have enabled a skilled artisan to make and use the *Salmonella* compositions claimed without undue experimentation.

Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejections under 35 U.S.C. § 103

The Examiner alleges that claims 1, 5-7, 11-15, 18-21, 23-27, 29, 33, 35-37, 42-44, 48-52, 54-56, 60, and 65 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Bermudes et al., (U.S. Patent Application No. 20050249706, dated 11/10/05, effective filing date 10/4/99) or Szalay et al (U.S. Patent Application No. 20050069491, dated 3/31/05, effective filing date 7/31/02), Francisco et al. 1993 (*PNAS*, 90(22): 10444-48), and Wu et al., 1996 (*Immunotechnology*, 2:21-36).

In reply, applicants traverse the rejection and submit that the present claims are not obvious. The presently claimed invention is directed to a composition for delivering an agent to a neoplastic cell of a solid tumor expressing a neoplasm-specific antigen, wherein the composition comprises an agent and an attenuated *Salmonella* or *Shigella* microorganism that has an antibody or fragment thereof on its cell surface that binds to a neoplasm-specific antigen on the surface of a neoplastic cell of a solid tumor. Another aspect of the claimed invention is directed to methods of treating a CEA-expressing neoplasia in a subject via administering a therapeutic composition of the attenuated *Salmonella* or *Shigella* microorganism of the invention, in the absence or presence of an agent.

According to the Examiner, Bermudes et al. teach an "attenuated strain of *Salmonella typhimurium* (VNP 200009) that may comprise effector molecules which are encoded by a plasmid or… nucleic acid…. [and] expressed in an attenuated tumor-targeted bacteria in the treatment of variety of cancer." The Examiner further alleges that Szalay et al. disclose the "availability of another strain of Salmonella… that may be genetically modified to target variety of cancer." However, as acknowledged by the Examiner, Bermudes et al. and Szalay et al. do not teach or suggest "expressing an antibody or an neoplasm specific antigen on the surface of the microorganism" (See Page 15, line 24 of Office Action dated July 9, 2008).

The Examiner also alleges that Francisco et al., teach "a method for displaying a functional scFv antibody fragment to the outer surface of *E. coli* microorganism…", while Wu et al. "provides guidance with respect to the sequences of anti-CEA diabody." Francisco et al. and Wu et al., however, do not teach a *Salmonella* microorganism that expresses on its surface an antibody or fragment thereof that binds to a neoplasm-specific antigen (such as CEA) on the surface of a neoplastic cell of a solid tumor.

In view of the publications discussed above, the Examiner alleges that "it would have been obvious for one of ordinary skill in the art... to modify the genetically modified attenuated strain of *Salmonella typhimurium* (VNP 200009 or SL7207) to express a functional scFv antibody fragment on the outer surface... that has *excellent* tumor homing properties." Applicants submit that the skilled artisan would not have had a reasonable expectation of success in obtaining the claimed composition in view of the combination of references cited by the Examiner. In particular, the skilled person would not have had a reasonable expectation of success of obtaining a *Salmonella* expressing a "functional" scFv. A skilled artisan would not have predicted that obtaining such a composition would be successful for several reasons. For example: a protein must express at sufficient levels to elicit an effect; a protein must not be degraded by the organism's intrinsic cellular machinery; a protein must be folded properly and be stable; a protein needs to be targeted properly to the cell surface; in the case of protein display, the protein must be adhered to the cell surface; once expressed on the cell surface of a *Salmonella* organism, the protein must be an active protein. Furthermore, one of ordinary skill in the art would have had no reasonable expectation that an antibody would be expressed on the surface of an organism, and subsequently would efficiently target a solid tumor, as alleged by the Examiner. For example, Phizicky and Fields (Exhibit C; *Microbiological Reviews* (1995) 59(1): 94-123) state that some of the "[d]isadvantages of phage display include the size limitation of protein sequence for polyvalent display; the requirement for proteins to be secreted from *E. coli*; and the use of a bacterial host which may preclude the correct folding or modification of some proteins. All phage-encoded proteins are fusion proteins, which may limit the activity or accessibility for binding of some proteins" (p. 104, 2nd column). These views are also shared by Van Criekinge and Beyaert (Exhibit B; see p. 3, 1st paragraph; *Biol Proced Online* (1999) 2(1): 1-38). In *KSR*, the Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739. Expressing a "functional" protein at the surface of an organism, such as *Salmonell*a, having tumor homing properties is not predictable for the reasons discussed above; thus, one of ordinary skill in the art would not have reasonably expected success in making and using the claimed composition of the invention. Therefore, the claimed invention is not obvious in view of the cited references.

Applicants have provided Theriot's paper (Exhibit D; *Ann Rev. Cell Dev Biol* (1995), 11: 213-39) which discloses differences between different types of pathogenic bacteria, such as whether they are internal or external pathogens relative to a cell. For example, the paper states, "Enteropathogenic *Escherichia coli* adhere closely to the epithelial cell apical surface and cause effacement of the microvilli… [that is] directed by the bacteria while they remain external to the host cell…" (p. 216, 3rd paragraph); "[i]n contrast to… bacteria that interact with host cells while remaining outside of them, a variety of pathogens actually live inside the cells of the infected host… one widely studied example of this class of bacteria is *Salmonella typhimurium*, which survives and multiples within a membrane bound compartment after it is phagocytosed by the cell." The paper distinguishes between *E. coli* and *Salmonella* on the basis of their cellular localization, and further establishes in the field that *Salmonella* is an intracellular organism (for example, see Medina and Guzman (2001) *Vaccine* 19(13-14):1573-80: "Salmonella are intracellular pathogens that remain restricted to endosomal compartment of eukaryotic cells, resisting non-specific killing mechanisms."). If the skilled artisan's aim was to achieve cellular entry, as in the case in the instant invention whereby entry into tumor cells is essential to obtaining a therapeutic effect, one of ordinary skill in the art at the time of filing would have opted for using an intracellular pathogenic bacterium (such as *Salmonella*) rather than an extracellular bacterium (such as *E. coli*) since an extracellular organism would remain external to a cell. One of ordinary skill in the art would have been discouraged from using an extracellular organism, and would not look to publications that utilize *E. coli* (for example, Francisco et al. (1993, *PNAS*, 90(22): 10444-48)) for guidance in constructing a composition for delivering an agent into a neoplastic cell of a solid tumor expressing a neoplasm-specific antigen, wherein the composition comprises an attenuated *Salmonella* or *Shigella* microorganism that has an antibody or fragment thereof on its cell surface that binds to a neoplasm-specific antigen on the surface of a neoplastic cell of a solid tumor.

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Guzman and Medina's as well as Theriot's distinction between the intracellular pathogen *Salmonella* and the extracellular bacterium *E. coli* discourages the use of extracellular pathogenic bacteria if intracellular localization is desired, and thus, in effect "teach

away" from using such pathogenic bacteria. Based on the teachings of the art at the time of filing, one of ordinary skill in the art would not have reasonably expected success in making and using the claimed composition of the invention. It would not have been obvious to the skilled artisan to modify the *Salmonella* organism described in Bermudes et al., (U.S. Patent Application No. 20050249706) by applying the "method for displaying a functional scFv antibody fragment to the outer surface of *E. coli* microorganism" described in Francisco et al. to generate a composition for delivering an agent into a neoplastic cell of a solid tumor expressing a neoplasm-specific antigen, wherein the composition comprises an attenuated *Salmonella* or *Shigella* microorganism that has an antibody or fragment thereof on its cell surface that binds to a neoplasm-specific antigen on the surface of a neoplastic cell of a solid tumor. The skilled artisan would recognize the difference between the use of an intracellular vs. an extracellular pathogenic bacteria in seeking entry into tumor cells. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

In conclusion, Applicants submit that it would not have been obvious to a person of ordinary skill in the art to generate a composition for delivering an agent to a neoplastic cell of a solid tumor expressing a neoplasm-specific antigen, wherein the composition comprises an agent and an attenuated *Salmonella* or *Shigella* microorganism that has an antibody or fragment thereof on its cell surface that binds to a neoplasm-specific antigen on the surface of a neoplastic cell of a solid tumor, and subsequently use the composition for methods of treating a CEA-expressing neoplasia, in the absence or presence of an agent.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection.

In view of the above amendments and comments, applicants request that the Examiner reconsider and withdraw the grounds for rejection and allow the application to issue. The Commissioner is authorized to charge any fees that might be due to Deposit Account No. 08-0219.

Respectfully submitted,

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